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Solving Medical Problems with BioMEMS

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A routine laboratory exercise for an undergraduate electrical engineering student is to build a simple electronic filter circuit and determine its frequency and transient response. During the exercise, the student exposes the circuit to a range of electrical signals and captures the voltage and current characteristics. The relationship between what the circuit is exposed to and how it responds allows for developing a transfer function that provides insight into how the circuit operates. This approach, which is the basis of systems identification, can be applied to an almost infinite number of cases spanning from engineering problems to social sciences, and its application to biology is not an exception (Figure 1). For example, when a cell is exposed to a certain drug, it may respond by changing its morphology or by secreting specific molecules that can be detected by specific assays. In this case, one can produce a transfer function that couples the drug dose (input) with cell response (output) to describe the basic operation of a cell, more specifically, whether the drug produces the intended outcome.

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There is a multidimensional parameter space for modulating a biological machinery. First, the type of stimulus can be biochemical, optical, electrical, or mechanical, each of which will lead to a different cellular response. Second, the temporal profile of the stimulus can be different, i.e., it can be constant or oscillatory. Finally, where the stimulus is applied, a specific location on the cell, in this case, can make a difference in the observed response. The ways in which a biological entity manifests its responses are quite complex. The stimuli can lead to changes in the regulation of certain genes, which in turn, result in the synthesis of specific proteins. These proteins may cause secretion of specialized molecules and alterations in cell morphology and intracellular processes.

For the past few decades, research has produced diverse tools to modulate and monitor the activity of cells and tissues. While these tools are widely used in the biological community, some scientific questions require more sophisticated platforms. For example, a majority of conventional modulation techniques are steady state in nature, i.e., cells are exposed to a nontime-varying stimulus profile. This constitutes an obstacle for providing insight into realistic cell responses, as almost all biological processes are highly dynamic. From the monitoring standpoint, most existing assays only offer end-point measurements and are not amenable to real-time data acquisition, thereby limiting the opportunities to more accurately examine the biological response. Aside from the difficulties associated with modulation and monitoring, an enormous challenge is to accommodate the isolated biological samples in a manner that maintains their in vivo-like properties, or at least, the properties that are relevant to the biological question in hand.

An ideal testing platform would seamlessly integrate components to accommodate, modulate, and monitor cells to better tap into biological phenomena. Over the last few decades, advancements in micro- and nanotechnology have provided unique opportunities to

address some of these challenges. For example, the ability to micropattern cells into an in vivo-like configuration can improve their viability and metabolic activity. Miniaturization of conventional assays to monitor cellular function has generated more rapid assays that consume fewer reagents and allowed numerous assays to be run in parallel, thereby, increasing throughput. The recent advances in modulation allows for optically coupled electrochemical stimulation of cells with previously unattainable spatial and temporal resolution.

While there is a rich set of nomenclature describing miniature platforms and techniques, including microfluidics, microdevices, and micro total analysis systems, they can all be listed under the umbrella term *biological microelectromechanical systems* (BioMEMS). The goal of this article is to discuss several aspects of an ideal integrated platform to study the biological response of cells/tissues, with an emphasis on disease mechanics and therapeutics development.

Modulating Cell Behavior

Much of the cell response (e.g., migration [1], tumor growth [2], development [3]) is defined by a particular cellular microenvironment, which is a function of multiple variables including mechanical (physical interaction between cells and their surroundings) and biochemical cues (signaling molecules and cytokines). The techniques of modulating cell behavior are dealt with before discussing the techniques for preserving in vivo-like attributes of cells.

Chemical Modulation

Over the last few decades, microfabrication techniques adopted from the microelectronics industry have been applied to manipulate liquids and biological entities at small length scales, thereby creating the field of BioMEMS. This rapidly expanding field has enabled schemes to control cell behavior that were previously impossible. Traditionally, cells have been exposed to soluble biochemicals such as cell signaling molecules, hormones, pharmaceuticals, and nutrients. These molecules activate specific receptors on the cell membrane, or within the cell, following internalization, leading to a cascade of events that determine cell behavior. Conventionally, the metered biochemicals are added using a micropipette. In addition to the tedious task to pipette varying concentrations to mimic a time-varying stimulus, a single-step addition of biochemicals produces a stimulation profile that decreases over time due to consumption of factors by the cell or via noncellular chemical degradation.

In general, the decrease in concentration over time cannot be accurately predicted, further complicating the determination of input–output relationship. Microfluidics technology offers the critical ability to perfuse cultured cells with a well-defined stimulus pattern, thereby facilitating stimulus–response analysis [4]. A simple scheme of creating a time-varying stimulus pattern is to use many-to-one channel junctions, where different biochemicals are proportionally mixed [Figure 2(a)]. A computer can conveniently prescribe arbitrary stimulus patterns composed of desired proportions of biochemicals. Such a system, for example, can be used to simulate nutrient concentrations in blood following fasting and

feeding. The cells that process and consume nutrients can then be exposed to periodic nutrient variations along with hormones, pharmaceuticals, or even biomolecules that appear during disease, with the goal of understanding the metabolic variations in various disease states, such as obesity or muscle wasting.

Perhaps, one of the most powerful advantages of BioMEMS device over traditional cell culture is the spatial and temporal control of concentration gradients at the microscale level [3], [5]–[8]. At these length scales, the fluidic flow is laminar, that is, the only mode of transport is through diffusion, unless extraordinary measures, such as chaotic mixers are incorporated [9]. This physical condition allows for establishing stable gradients of chemoattractants that play a role in how cells respond during inflammation or infection [10], [11]. The insight from these studies can help us understand the ways the cancer cells invade healthy tissue and the mechanisms of immune cells attacking foreign bodies.

Electrical Stimulation

Some cells, such as neurons and endocrine cells (e.g., pancreatic beta cells), respond to an electrical stimulation by neural transmission of signals and secretion of hormones (e.g., insulin). The ability to electrically induce cells and track their electrical activity has been the basis of electrophysiology, which is directed toward understanding how a network of neurons collectively executes high-level functions such as memory and cognition. The challenge here is to be able to individually stimulate cells. Traditionally, neurons have been selectively induced using microwires, which severely complicated the parallelized and independent stimulation of multiple cells. Micropatterned electrodes on culture platforms [12], or more exotic nanoprobe [13], coupled with microfluidics for precise temporal and spatial exposure to biochemicals are powerful means to stimulate single neurons [Figure 2(b)].

Optical Methods

Recently, additional sophisticated stimulation tools have become available. Using a clever combination of genetics and optical methods, called *optogenetics* [14], investigators have modified the genetic machinery of different cell types to synthesize nonnative light-sensitive proteins (e.g., channel rhodopsins that originate from unicellular organisms such as green algae). These modified cells can then respond to light stimulation by modulating the inward/outward flow of ions through their cell membranes and consequently result in a unique cell behavior. An advantage of this technique is the ability to stimulate cells with very high temporal and spatial resolution, which has important implications in the field of neuroscience. Although platforms that combine optogenetic tools (enable by arrays of onboard optical sources) and microfluidics are yet to be seen, we expect that this combination of techniques will yield many new and exciting opportunities for tapping into cell function.

Mechanical Perturbation

Another stimulation mode is mechanical perturbation, which affects the cell response in various ways ranging from changes in morphology to gene expression [15]. For example, endothelial cells coating the veins respond to blood flow by aligning along the direction of

flow. It has been difficult to probe cells mechanically in a controllable fashion due to the absence of adequate tools. Microfluidics has been an enabling tool for applying quantifiable fluidic shear forces on cells, as channel dimensions can be precisely engineered to mimic complex vasculature and control flow rates [Figure 2(d)]. Apart from fluidic forces, variations in the substrate mechanical stiffness have been shown to dictate cell response [16]. A striking example of this is stem cells differentiating into adipocyte-like (fat) cells and osteoblast-like (bone) cells on soft and hard surfaces, respectively. Similarly, it has been observed that mesenchymal stem cells and bone marrow stromal cells tend to migrate toward mechanically stiffer surfaces [17], [18].

Monitoring Cellular Behavior

Ultimately, the power of modulation platforms is determined in part by the capabilities of the complementary platforms for monitoring biological response. The requirements for monitoring cellular behavior are the same as those for stimulation (i.e., temporal and spatial resolution), and the relative importance of these parameters depends on the application. For example, temporal resolution is important if one is interested in studying the neural firing rate, while spatial resolution is important when localizing increased neural activity. Cells have a multitude of ways to exhibit their response to a prescribed perturbation. It is important to choose a readout that is most relevant to the biological question one is attempting to answer.

Monitoring the Morphology

The most traditional readouts have involved monitoring the morphology and structural features of cells (i.e., change in shape and size), intracellular products of synthesis and metabolism (e.g., metabolites and secreted molecules), and changes in genes expressed. Morphological changes can be detected by simply observing cells under a microscope. While an experienced person can differentiate various cellular states (such as a healthy versus an unhealthy cell), it is difficult to conclusively identify a cellular state with this method alone. For example, while two cells look similar in morphology, one may be significantly less viable. Such information can be obtained through biochemical means.

Typically, special fluorescent dyes can be used to interrogate whether a cell is alive or dead. There is now a rich and expanding library of such dyes that are used for shedding light onto cellular processes including metabolism, differentiation, and proliferation. Because the majority of optical assays require bulky external equipment, there is a trend toward incorporating optical detection schemes on miniaturized platforms [19] [Figure 2(c)]. Subtle changes in morphology captured by high-content imaging can reveal key information about cellular activity, such as specific changes in cytoskeleton (the truss structure that maintains cellular form) and can offer information about stem cell fate [20]. Complementing the integrated microoptofluidic systems with the techniques of high-content imaging enable a variety of onchip measurements as well as create highly portable devices that can be used in remote settings.

Cell Secretion and Cell Surface Changes

Cells also respond to stimuli by secreting molecules that regulate their own activity as well as nearby or distant cells. For example, certain cells, when they detect an intruder, synthesize and secrete signaling molecules (e.g., interferon gamma) to alert the surrounding cells. There are established biochemical techniques that quantify the secreted proteins based on antibody or other ligand-binding schemes. Microfluidics-based assays show an assurance in improving the detection of such measurements.

A promising advancement that builds upon unique strengths of microscale geometries is the production of reproducible water-in-oil droplets [21] [Figure 2(a)]. The droplets serve as small reaction chambers that can encapsulate cellular secretions, assay reagents, and even single cells. The applications of this method include colorimetric detection of zinc in secretions from pancreatic islets [22] and fluorometric detection of cytokine secretions from encapsulated cells [23]. Electrochemical sensors can also be miniaturized to detect cellular secretions [24]. Cells exhibit changes in their surface structure via expression of different proteins, which are also commonly used for identifying cell types. There have been advances in detecting such surface markers on a single-cell level by combining microfluidic droplets and biomolecular detection methods [25]. A major challenge for monitoring cellular secretions or surface changes, however, remains as the ability to do continuous measurements.

Electrical Activity

The response of neurons is largely characterized by their electrical activity, which in turn can define normal versus abnormal activity. To probe in detail the activity of neurons, it is necessary to have electrodes that can focus on a single neuron [Figure 2(c)]. The challenge is that, as the surface area of the electrode decreases, its sensitivity begins to decrease as well. Nanostructured surfaces with high effective surface areas have alleviated this problem [26]. Microelectrode arrays have also benefited studies outside neuroscience, such as recordings of cardiac action potentials to evaluate pesticide toxicity in a high-throughput manner [27]. Recent studies have also correlated changes in electrical impedance of stem cells to their differentiated state [28], exemplifying how nontraditional readouts can provide additional information about cell behavior.

Genomic Expression

The above readouts are all palpable external to the cell. There are unique challenges associated with trying to monitor intracellular processes, such as expression of certain genes. Conventionally, messenger RNA (a set of intermediate molecules that carry a transcribed form of the gene to the ribosome to be made into a protein) is extracted from the cells and amplified. This process virtually becomes impossible when one wants to probe gene expression in many individual cells or group of cells.

One approach has been to modify the cells by introducing a synthetic DNA that produces an externally detectable signal in response to changes in some part of genetic machinery. A popular example involves the use of fusion proteins that contain green-fluorescent protein. These reporter cells can then be micropatterned into arrays enclosed with microfluidic

channels to be exposed to a library of stimuli, leading to changes in cell response that can be readily observed in fluorescence [29] [Figure 2(c)]. This technology, coupled with onchip optical detection schemes, can be very powerful.

Developing Bioinformatics

The ability to modulate and monitor cell response in high throughput creates a new challenge: the necessity to process large amounts of data, preferably, in real time. This need has led to the development of complex bioinformatics algorithms [30]. Referring back to the notion of systems identification approach, the objective is to acquire adequate input–output data points at different time points to create a transfer function, which can then be used for 1) revealing intracellular mechanisms and 2) predicting a set of cellular responses (output) in response to a specific set of input. An accurate transfer function could then be used to run many experiments via computer simulations, saving enormous amounts of time and money by reserving the biological experiments for ultimate in vitro, and eventually, in vivo validation.

Accommodating Environments

BioMEMS technology offers multiple design parameters to create a more physiologically relevant environment, promoting cells to function similar to their in vivo state (Figure 3). We will discuss the differences between traditional and microscale cell culture techniques and the factors to be considered to obtain proper cell growth and normal cell functions inside BioMEMS devices.

BioMEMS for Generating Physiologically Realistic Cell Culture Environments

The flow over cells in microfluidic channels introduces shear stress. Although low shear stress can damage certain cell types, other cells require shear stress to function properly, such as vascular endothelial cells that align themselves in response to blood flow [31]. Careful modulation of flow rate and shear stress inside BioMEMS devices is thus a key factor for improving cell viability and function.

A key parameter that dictates in cell viability and function is the type of material used in BioMEMS devices. A variety of materials, including polydimethylsiloxane (PDMS), polystyrene, polycarbonate, silicon, SU-8, and glass, are available for building application-specific BioMEMS platforms. Each material comes with its own advantages and potential drawbacks. For example, PDMS, the most commonly used material for construction of BioMEMS devices that involve cell culture, offers great versatility for prototyping devices and exhibits reasonable biocompatibility. However, the inherent hydrophobicity of PDMS makes it susceptible to nonspecific adhesion of proteins and to absorbing nonpolar molecules into its polymer matrix, thereby limiting its use in biochemical assays.

Surface treatment techniques such as oxygen plasma treatment, matrix protein coatings, and various surfactants coating partially mitigate hydrophobicity and the related challenges. Glass devices are significantly more suitable for biochemical assays; however, their fabrication is generally not trivial. Increasingly, evidence suggests that nanoscale surface topology of a specific material is as important as the material itself in dictating cell behavior. For example,

a recent demonstration of a tissue constructed using nanotopographical cues mimicked the ventricular organization of heart and displayed electrophysiological activity similar to that of native tissues [32].

3-D Cell Culture

In animal tissues, cells reside in a three-dimensional (3-D) space surrounded by neighboring cells and an extracellular matrix (ECM). Conventional two-dimensional (2-D) cultures (e.g., cells cultured on planar geometries), therefore, may not accurately represent the in vivo state. Various 3-D cell culture systems are available for researchers to create a more in vivo-like environment. Typically, cells are encapsulated inside a 3-D matrix of hydrogel. Several hydrogels with unique chemical and physical properties exist; however, incorporating a hydrogel scaffold into a BioMEMS device is very challenging. While ultraviolet (UV)-curable hydrogels allow gel formation by simply exposing a microfluidic device to a UV source, there is a concern about the adverse effects of UV light on cell viability and function. Alginate, on the other hand, can polymerize upon contact with cationic solutions; however, slow mixing in microfluidic channels can complicate homogenous gel formation.

Natural hydrogels, such as collagen or Matrigel, can be injected into a device and polymerized by slightly increasing the solution temperature, provided that the devices are kept cold beforehand to prevent premature gel formation. In addition, natural tissues consist of different types of cells, and therefore, in many cases, a coculture is necessary to elicit realistic cell function. For example, hepatocytes in the liver coexist with the supporting cell types such as Kupffer cells. Selective micropatterning of different cell types on a surface enables the creation of complex coculture systems and improves the performance of 2-D cell culture systems dramatically. However, extending these techniques to a 3-D geometry requires precise spatial manipulation of cells and is still a significant challenge to creating robust 3-D coculture systems.

Cell Seeding

The small dimensions of BioMEMS devices make uniform cell seeding a challenge. In addition, device surfaces often need to be treated with ECM proteins to promote stable adhesion of cells. Microfabrication technology allows for selective micropatterning of cells on a surface. The surface can be treated with chemical patterns that promote or repel cell adhesion in defined areas. Surface patterning techniques include micro contact printing, UV lithography, microfluidic patterning, and stencil-based patterning. While these approaches are limited to 2-D, several techniques for shaping hydrogels into 3-D shapes exist, including micromolding, UV photopolymerization, microfluidic-based patterning, and direct printing [33].

Integration of Components

Miniaturization allows the integration of components with different functions so that cell seeding, cell culture, modulation, monitoring, and analysis can be achieved on a single chip with high efficiency (Figure 4). However, exploiting this advantage to its full extent requires careful consideration of physical phenomena inside microscale systems.

Scale Up

The common approach for high-throughput platforms is to build an array of microscale wells interconnected via fluidic channels. Microfabrication techniques allow for highly integrated arrays with fluidic control for individual wells. A prominent example is the microfluidic system developed by Quake, consisting of 2,400 individual wells controlled by 7,233 valves, which was used to study the binding of transcription factors [34]. Less extensive microfluidic arrays have been developed for mammalian and bacterial cell culture with the capabilities approaching 384 multiwell plates that are traditionally used for high-throughput experiments.

Flow Control

Large-scale microfluidic systems complicate manual flow control, as nanoliter volumes need to be manipulated within microchannels. For this purpose, various miniaturized pumping and valving schemes have been introduced. The most common method of pumping fluid is the use of an external peristaltic or syringe pump. This method creates a parabolic velocity profile inside the channels, which limits uniform delivery of analytes within a channel. An alternative with a more uniform flow profile is electroosmotic flow, where the surface-induced ions displace the liquid when an electrical potential is applied at the ends of a channel. Other nonconventional pumping techniques include passive pumping, such as gravity-driven flow [35] and surface tension-driven wicking [36]. As these techniques do not typically require complicated external circuitry to operate, their integration into microfluidics could facilitate their use in resource-limited settings.

An essential requirement for fluidic control is the ability to precisely guide flow within a mazelike microfluidic structure. Following the demonstration of a PDMS-based pneumatic microvalve [37], most fluidic platforms have employed such valves for flow control. This method uses a compliant PDMS chamber adjacent to the microfluidic channel containing the fluid to be manipulated. Applying negative or positive pressure to the deformable PDMS chamber constricts or relieves the adjacent channel, thereby controlling the liquid flow. This technique is now applicable to highly complex microfluidic devices as well those that are simple, such as handheld devices or screw-actuated valves. Another interesting, but less widely utilized, method uses Braille pin displays to generate peristaltic flow [38].

Although microvalves can be actuated in various modes, including pneumatic [37], electrical [39], optical [40], or magnetic [41] with unique strengths and weakness, the universal challenge has been the excessive complexity of fluidic control. Basic passive flow control is possible by sizing cross-sectional areas and the pressure drops through channels. Simpler techniques are imperative to translate BioMEMS devices into clinical settings or biology laboratories.

While the laminar flow phenomenon in microfluidic channels is advantageous for numerous applications, low Reynolds number flows are not conducive to efficient mixing due to the absence of turbulence. Approaches to improve mixing efficiency include 1) a chaotic mixer created by etching a bas-relief pattern on the floor of a microchannel [42], 2) using magnetic

particles to enhance mixing inside a microfluidic device [43], and 2) electrowetting-based mixing of droplets residing on surfaces [44].

Interface with External Components

Miniaturization creates challenges in all aspects of technology development, including detection, fluid manipulation, and stimulation. Another difficulty is interfacing the BioMEMS devices with external components such as conventional pumps, electronic instrumentation, and optical equipment. Typically, external frames, manifolds, and electrical, pneumatic, and optical setups are used for operating BioMEMS devices. Smaller sample sizes require higher detection sensitivity and, to this end, the sensors have been integrated onto chips for more immediate detection.

Advanced flow control schemes that take advantage of micro- and nanoscale phenomena are expected to reduce the dependence on bulky external solenoids and pressure sources. As mammalian cell culture requires careful regulation of temperature and CO₂ levels, BioMEMS cell culture systems operating outside controlled environments face additional challenges. Finally, a major design question is whether to contain complexity within the BioMEMS device or within its peripheral components. Although complex BioMEMS devices may reduce the dependence on external components, reusability issues may make them less cost effective.

Application Platforms

The combination of the aforementioned BioMEMS tools and techniques allow for the development of platforms to study and control a milieu of biological phenomena. Several application areas to be highlighted have particularly attracted attention from the scientific and industrial communities.

Cell Separation

The ability to capture and enrich specific cell types from the blood stream is of huge medical importance. Physical properties such as size, density, and charge, or affinity to specific ligands, can be used to sort cells. With the ability to precisely control the flow, BioMEMS devices offer advantages over conventional cell-separation techniques such as filtration, centrifugation, and fluorescence-activated cell sorting. One prominent application of cell separation technique is the isolation of circulating tumor cells (CTCs) for diagnostic and treatment purposes, using a microfluidic device coated with antibodies against tumor cells [45]. Diverse adhesion molecules have been used for cell isolation in microchips, including peptides, proteins, aptamers, and nanostructured surfaces.

Stem Cell Differentiation

Stem cells are characterized by the capability to undergo mitotic cell division, resulting in self-renewal and differentiation into specific cell types. BioMEMS devices are ideal tools for reproducing the complex microenvironment of stem cells, inducing differentiation into specific cell types. Various aspects of cellular microenvironments and their effects on differentiation efficiency and cell function have been studied in microchips, such as soluble

factors, ECM interactions, cell–cell interactions, mechanical signals, and cellular aggregate size. It is expected that these studies can provide critical insight into the optimal parameters for attaining efficient differentiation of stem cells into functional cell types for therapeutic and drug-development applications.

Artificial Organ-on-a-Chip

There have been a large number of efforts to capture the distinct characteristics of specific organs and build an in vitro system mimicking those features. These characteristics include 3-D geometries, cell–cell or cell–matrix interactions, concentration gradient of chemicals, and blood flow. For example, the liver is responsible for the biotransformation of external compounds, and recreating the function of the liver in vitro would be a tremendous achievement in biomedical engineering. There have been attempts to culture hepatocytes in a microfluidic device, re-create the oxygen concentration gradient that is known to exist in the liver [46], form spheroid-like 3-D construct of hepatocytes in a microfluidic device [47], and micropattern hepatocytes with fibroblasts [48]. Many of these attempts were reported to result in the enhancement of liver-specific metabolic activity. Other organs have been re-created as an organ-on-a-chip. These organs include lung [49], gastrointestinal tract [50], and vascular networks [51]. Recently, Huh et al. reproduced the mechanical movement of alveolar space of the lung, which was reported to enhance the inflammatory response of the lung to nanoparticles [49].

Drug Screening

BioMEMS devices can be used as in vitro platforms for various stages of the drug-development process, such as lead compound identification, toxicity/efficacy screening, and the study of drug-delivery mechanisms. In particular, BioMEMS is useful for creating differential conditions, such as a range of drug concentrations, in a single implementation. An interesting application of BioMEMS technology is the reproduction of whole-body responses to drugs. After a drug is administered, it goes through a complex process of absorption, distribution, metabolism, and elimination, which cannot be reproduced with conventional cell culture methods using a single cell line. A BioMEMS device, termed as *animal-on-a-chip*, has been developed to reproduce the dynamics of drug action in the human body. The microchip consists of multiple chambers representing organs, interconnected with fluidic channels representing the blood flow.

The main advantage of using BioMEMS is that the blood-flow pattern of the human body can be reproduced accurately, and the whole-body pharmacokinetics can be tested in vitro. It has been demonstrated that these devices can reproduce the metabolism-dependent toxicity of naphthalene and an anticancer drug, Tegafur [52], [53].

Fundamental Biological Studies

BioMEMS has been used as in vitro platforms to study various biological phenomena in a more controlled manner. Conditions mimicking a disease state or cellular environment can be better reproduced with microtechnology. The notable examples of this kind of study include chemotaxis, biomechanics, angiogenesis [54], developmental biology, and single-cell genetic networks. With microtechnology, it becomes easier to decouple a specific

environmental factor from others and study the effect of a single factor on cell behavior. Similar to the drug-screening application, it is also possible to create multiple conditions in a single implementation to study the combinatorial effect of environmental factors.

Conclusions and Future Directions

The BioMEMS technology offers new possibilities for modulating, monitoring, and accommodating biological entities in unprecedented ways. These novel techniques allow researchers to create a more physiologically relevant environment, which promotes more realistic responses from cultured cells. In this article, we reviewed the recent trends and advancements in micronanotechnologies related to disease studies and therapeutics development. While numerous proof-of-concept studies exist for BioMEMS devices to make an impact in biology and medicine, we are still far from the acceptance of BioMEMS tools by traditional biology researchers, industrial scientists, and clinicians. Complexity and unreliability in operating BioMEMS devices are two of the major obstacles preventing the widespread use of these tools. We believe that there is a need for simplifying and standardizing BioMEMS tools, as well as training biologists and clinicians for them to benefit from the advantages of BioMEMS techniques. The BioMEMS field is still growing rapidly, and we expect to see real-world applications of BioMEMS devices in the near future.

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FIGURE 1. Systems identification techniques to analyze cellular processes.

FIGURE 2. Comparison of conventional and BioMEMS approaches to monitor and modulate cellular activity: (a) biochemical, (b) electrical, (c) optical, and (d) mechanical.

FIGURE 3.

Key parameters that play a role in obtaining an in vivo-like cellular response.

FIGURE 4. The key components of an integrated BioMEMS platform to monitor and modulate cellular activity.